DESIGN AND PROCESSING OF SOLID DISPERSIONS IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

Solid dispersions have already been described over more than 50 years ago in scientific literature to improve solubility of poorly water soluble drugs. With the increasing number of new poorly soluble drug candidates discovered at early industrial stages, the knowledge about these metastable amorphous systems has significantly improved over the decades. While in the early days of solid dispersions pharmaceutical companies were rather very reluctant to invest in corresponding manufacturing technologies, nowadays a significant number of market drug products has been developed based upon this not novel drug delivery principle. The presentation will give an overview about properties of solid dispersions, industrial screening and manufacturing methods and the biopharmaceutical implications.

Keywords: Solid dispersion, amorphous, solubility, metastable, drug delivery

INTRODUCTION

With the dramatic increase in poorly soluble drug candidates (Biopharmaceutical Classes I and IV) from drug discovery organisations in industrial drug development, scientists had to look for innovative approaches to improve their aqueous and in-vivo solubilities. Beside salt formation, particle size reduction (e.g. milling, micro- or nano-nizing), formation of Cyclodextrin complexes or incorporation of poorly soluble drug candidates in microemulsion systems (SEDDS, SMEDDS), the destruction of the crystal lattice in a suitable matrix and thus formation of a metastable amorphous system or solid dispersion has in the meantime turned out to become one of the most attractive approaches in industrial drug development.

RESEARCH CONCEPT

Delivery principle

The interest in solid dispersions has started in the 1960s already and a first definition was given by Chiou and Riegelmann: " A solid dispersion is a dispersion of one or more active ingredients in an inert carrier or matrix by the melting (fusion), solvent, or the melting-solvent method [Chiou, Riegelmann, 1971]. With regards to the metastable nature of these ideally amorphous systems, the question that researchers had to solve was always the physical stability, preventing recrystallization of try at least to delay such an event until the end of the shelf-life of a marketed drug product. Such a stabilization could be a solubility, thermodynamically based concept or the formation of a solid dispersion where the dispersed molecules of the poorly soluble drug candidates are kinetically immobilized, e.g. by adjusting high glass transition temperatures for the solid dispersion using the principles described by the Gordon-Taylor equation with w1 and w2 representing the weight fractions e.g. of drug and matrix/polymer and Tg1 and Tg2 their corresponding glass transition temperatures (Tg is then the glass transition temperature of the solid dispersion).

Gordon-Taylor equation

Equation 1

$$Tg = \frac{w_1 Tg_1 + K w_2 Tg_2}{w_1 + K w_2}$$

Nowadays solid dispersions are divided into 3 different categories or generations – starting in the early daysof the 1st generation with crystalline carriers (e.g. Urea, Fructose), moving later to polymeric carrier based (2nd generation) and then more recently to those of the 3rd generation including surface active carrier types.

Screening approaches

Details about different types of amorphous systems will be discussed during the presentation and screening concepts discussed (e.g. solubility in liquids, use of Hansen solubility parameters, DSC technique, other methods). Supportive modern analytical technologies will be briefly mentioned (e.g. SEM, TEM; micro Raman technique [Karavas, Georgarakis, Docoslis, Bikiaris, 2007]., solid stage NMR

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Manufacturing technologies

Over the past decades a couple of different manufacturing technologies have been applied. Generally the most prominent approaches are either based upon melting (e.g. hot melt-extrusion HME) or solvent based (e.g. spray drying, spray granulation). During the presentation further technical details and a scale-up experiment will be discussed..

Biophamaceutical aspects

An increase in aqueous solubility by forming a solid dispersion can improve drug absorption and thus the bioavailability of a poorly soluble drug significantly. Nevertheless it needs to be considered that vertain drugs have a high tendency to crush out or precipitate once the solid dispersion reaches the gastrointestinal tract. Therefore formulation scientists need to test solid dispersion prototype formulations also with regards to their precipitation robustness. Addition of surfactant-type carriers might improve the robustness significantly. Also such aspects have to be routinely screened nowadays,

RESULTS

The examples provided during the presentation will demonstrate how to develop solid dispersions by screening the right formulations and selecting the right manufacturing technology at an industrial scale including scaling-up and

DISCUSSION

The presentation explains the evolution of solid dispersion formuations over the last 50 years and how it is possible nowadays to develop stable and better up-scalable solid dispersions than ever before.

CONCLUSIONS

Solid dispersions are an attractive modern approach to deliver poorly soluble (“brickstone”) drugs successfully in an industrial environment. This has led to the market introduction of multiple products helping to significantly improve patients` lives.

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I would like to thank all the great scientists from which I learned a lot about solid dispersions over the years at Lilly, Novartis and Roche

NOMENCLATURE

SEDDS	self-emulsifying drug delivery system
SMEDDS	self-microemulsifying drug delivery system
SEM	scanning electron microscopy
TEM	transmission electron microscopy
Tg	glass transition temperature
W1, w2	weight fraction

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